059102

PROPOSED DATA PRESENTATION TO THE HAZARD I.D. SARC

Chemical Name: Chlorpyrifos-methyl

Date Submitted: October 2, 1997

I. DIETARY

1. ACUTE DIETARY (ONE DAY)*

Type of Study Proposed: Rabbit developmental toxicity, R-F study **Guideline #:** §83-3(b)

MRID No.: 099640, 242150

Executive Summary: In a prenatal developmental toxicity study conducted in rabbits (10/group) (MRID 099640, 42150; Doc. No. 001571, 002632), technical chlorpyrifos-methyl was administered by gavage in corn oil at doses of 4, 8, or 16 mg/kg/day on gestation days 6-18. The maternal NOEL was 4 mg/kg/day, based upon 20% decreased food consumption during treatment at the maternal LOEL of 8 mg/kg/day and above, with posttreatment recovery. The DER also reported the developmental NOEL to be 4 mg/kg/day, based upon a decreased number of corpora lutea, surviving fetuses and number of implantations at 8 mg/kg/day (the developmental LOEL) and above. Upon reexamination of the cesarean section and fetal data, no treatment-related fetal findings were identified. In the preliminary range-finding study in rabbits that was conducted to establish dose levels for the main developmental studyin rabbits, 8, 16, or 32 mg/kg/day was administered by gavage to rabbits for 14 days. Plasma ChE levels were measured at day 1 and 13 of study, and were found to be decreased at 16 mg/kg/day and above by day 1. This information was not reported in the original DER. (1976)

Dose and Endpoint Proposed for Consideration: In a range-finding study, plasma cholinesterase was decreased in rabbits after one day of dosing at 16 mg/kg/day, with a NOEL of 8 mg/kg/day.

Comments about Study/Endpoint: Toxicity (plasma cholinesterase inhibition) was established after one oral dose of chlorpyrifos-methyl. This endpoint has been observed in human studies.

There is a lack of confidence in the scientific validity of the developmental toxicity endpoint(s) defined for this study; therefore, they were not selected for use in the acute dietary risk assessment.

It is noted that the acute neurotoxicity study does not provide much additional information, since neuropathology was observed only after a dose of 5000 mg/kg in chickens. No acute neurotoxicity study in rats was submitted by the Registrant.

Risk Assessment for Acute Dietary Required: __X__ YES _____NO

** This risk assessment may be necessary for types of population groups [Females 13+ years as well as General Population (including infants and kids)] depending upon the type of study/dose/endpoint used.*

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2. CHRONIC DIETARY [Reference Dose (RfD)]

Type of Study: 2-year feeding study in dogs **Guideline #:** §83-1(b)

MRID No.: 099642, 242154

Executive Summary: 99.68% chlorpyrifos-methyl was administered in the diet to purebred beagle dogs (7/sex/group) at dietary levels of 0.03, 0.10, 1.0, or 3.0 mg/kg/day. There were no effects on body weight gain, food consumption, ophthalmology, clinical signs, hematology, urinalysis. Plasma and RBC cholinesterase activity was decreased approximately 30% at 1.0 mg/kg/day and above, peaking at study week 26; RBC cholinesterase measurements had returned to control levels by week 39. Brain cholinesterase activity was not affected at study termination. By the 26-week interim sacrifice, there was an increase in the relative liver weight and relative thymus weight at 1.0 mg/kg/day and above. After 78 weeks of treatment, liver enzymes (SAP and SGPT were slightly increased at the HDT of 3.0 mg/kg/day. Liver histopathology (minimal centrilobular hepatocyte vacuolation) was observed in only one animal at 3.0 mg/kg/day. The systemic NOEL was 1 mg/kg/day, based on an increase in SAP and SGPT and an increase in liver-to-body weight ratio at 3.0 mg/kg/day. The cholinesterase NOEL was 0.1 mg/kg/day, based on significant plasma (and transient RBC) depression at 1.0 mg/kg/day.

Dose Proposed for Consideration: NOEL = 0.1 mg/kg/day, based on RBC and plasma ChEI at the LOEL of 1.0 mg/kg/day.

Uncertainty Factor(s) Proposed for Consideration: 10

Proposed RfD: 0.01 mg/kg/day

Comments about Study/Endpoint/Uncertainty Factor(s): The RfD document states that only a 10-fold UF was added for "inter- and intraspecies" variability, and no further explanation is provided. It is speculated that the data from the study in humans was considered (MRID 099639, 242150). In that study, 94% chlorpyrifos-methyl was given by capsule at a daily dose of 0.1 mg/kg for 28 days. There was no effect on hematology, urinalysis, or plasma and RBC cholinesterase activity.

II. OCCUPATIONAL / RESIDENTIAL EXPOSURE—DERMAL

DERMAL ABSORPTION No dermal absorption study was available

Comments about Dermal Absorption: The dermal studies were not particularly useful, since the 3-week rabbit study did not identify depressed ChE, the 4/17 day rabbit dermal study and the human dermal study were conducted with 60% chlorpyrifos-methyl in xylene, and a dermal sensitization

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study in humans was conducted with 2% a.i. chlorpyrifos-methyl in 9:1 DPM:Tween 80.

There are no adequate comparative data available in the same species, between different routes of administration. It is noted that the human sensitization study demonstrated "moderate" plasma and RBC ChE inhibition after 2 exposures to a 10% concentration (i.e., a very small dermal dose of the test substance). Due to the lack of adequate data and due to evidence indicating that chlorpyrifos-methyl is readily absorbed through human skin, 100% dermal absorption (equivalency to oral dosing) must be assumed as a conservative default.

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1. SHORT-TERM DERMAL (1 - 7 days)

Type of Study Proposed: Rabbit developmental toxicity, RF study **Guideline #:** §83-3(b)

MRID No.: 099640, 242150

Executive Summary: see above

Dose and Endpoint Proposed for Consideration: 8 mg/kg/day (NOEL), based on plasma cholinesterase inhibition in rabbits after one dose

Comments about Study/Endpoint:

Risk Assessment for Short-Term Dermal Exposure Required: ___X___ **YES** _____**NO**

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2. INTERMEDIATE-TERM DERMAL (1-Week to Several Months)

Type of Study Proposed: Rabbit developmental toxicity, R-F study **Guideline #:** §83-3(b)

MRID No.: 099640, 242150

Executive Summary: See above

Dose and Endpoint Proposed for Consideration: 8 mg/kg/day (NOEL), based on plasma cholinesterase inhibition in rabbits after one dose and at 13 days

Comments about Study/Endpoint: Other short term studies (e.g., 3-week dermal rabbit or 14-day oral study in rats) did not contain conclusive results regarding cholinesterase inhibition.

Risk Assessment for Intermediate-Term Dermal Exposure Required: __X__ **YES** ____ **NO**

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3. LONG-TERM DERMAL (Several Months to Lifetime)

Type of Study Proposed: 2-year feeding studyin dogs (RfD study) **Guideline #:**

MRID No.: 099642, 242154

Executive Summary: See above

Dose and Endpoint Proposed for Consideration: 0.1 mg/kg/day (NOEL), plasma/RBC ChEI

Comments about Study/Endpoint: No long-term dermal study was available.

Risk Assessment for Long-Term Dermal Exposure Required: __X__ **YES** _____**NO**

III. OCCUPATIONAL / RESIDENTIAL EXPOSURE—INHALATION (ANY-TIME PERIOD)

Type of Study Proposed: No appropriate study was available. **Guideline #:**

MRID No.:

Executive Summary:

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Dose and Endpoint Proposed for Consideration:

Comments about Study/Endpoint: The only submitted inhalation study using technical grade chlorpyrifos-methyl is the acute LC50 study in rats. In this study, 4 hours of exposure at 0.67 mg/L resulted in no LC50 determination. Since the study DER could not be located, no other information on the toxicity by inhalation was identified.

Risk Assessment for Inhalation Exposure Required: _____ YES ___X___NO

ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Chlorpyrifos-methyl

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral (rat)	099638, 242152	LD_{50} = 2140 mg/kg (M); 1630 mg/kg (F) (94% a.i.)	III
81-1	Acute Oral (guinea pig)	099638, 242152	LD_{50} = 2250 mg/kg (94.0% a.i.)	III
81-1	Acute Oral (chicken)	099638, 242153	LD_{50} = 7532 mg/kg or >8000 mg/kg in 2 separate studies (95.8% a.i.)	IV
81-2	Acute Dermal (rabbit)	099638, 242152	LD_{50} > 2000 mg/kg (94% a.i.)	III
81-3	Acute Inhalation	256616	LC_{50} > 0.67 mg/L for 4-hrs (94% a.i.)	II
81-4	Primary Eye Irritation	099638, 242152	Slight irritation, recovered (90-94% a.i.)	III
81-5	Primary Skin Irritation	099638, 242152	Irritation of intact and abraded skin after 4-7 or 3 days of exposure, respectively (94.0% a.i.)	III
81-6	Dermal Sensitization	42191907	Positive for 62.2% a.i.	
81-8	Acute Neurotoxicity	099639, 242153	Positive delayed neuropathology at 5000 mg/kg (equivocal at 2500 mg/kg) (95.9% a.i.)	

Chemical: **Chlorpyrifos-methyl (PC Code: 059102)** DRAFT
From: Susan Makris (OP FQPA Subcommittee) October 2, 1997

The following evaluation of the chemical chlorpyrifos-methyl is provided to address FQPA considerations on the sensitivity of infants and children.

Summary of available neurotoxicity data:

A 1979 acute delayed neurotoxicity study (MRID 099639, 242153) was performed in the hen. The study was positive for delayed neurotoxicity at a dose of 5000 mg/kg, where 3/10 hens had sciatic nerve histopathology, and 4/10 hens showed positive vacuolation or demyelination and swollen fragmented axons in the spinal cord. At 2500 mg/kg, the findings were equivocal since 1/10 hens showed vacuolated neurilemmal sheets and granular fragmented axons.

In a guideline 90-day neurotoxicity study in chickens (MRID 072888; Doc. No. 00438), administered at doses of 5, 50, or 500 mg/kg/day, no delayed neurotoxicity was observed up to a dose of 500 mg/kg/day. The systemic LOEL for this study was 500 mg/kg/day, based upon decreased body weight and egg production, and the systemic NOEL was 50 mg/kg.

No acute or subchronic neurotoxicity studies in the rat were submitted by the Registrant.

There were no indications of effect on brain weight, and following processing of tissues without perfusion, no effects on the histopathology of the brain or peripheral nervous system were observed in any of the guideline subchronic or chronic studies in which these parameters were measured.

Summary of reproductive and developmental toxicity:

In a three-generation reproduction study in rats (MRID 099640, 242150; Doc No. 001571, 002333), chlorpyrifos-methyl (94%) was administered at dietary concentrations of 1.0 or 3.0 mg/kg/day). A parental systemic NOEL was not identified, since RBC and plasma cholinesterase were inhibited at the LDT of 1.0 mg/kg/day. The reproductive NOEL was 1.0 mg/kg/day, based upon a slight decrease in the fertility index observed at the reproductive LOEL of 3.0 mg/kg/day. There was no discussion in the DER of toxicity to the offspring, but cholinesterase inhibition was apparently not measured in pups. (1975)

In a prenatal developmental toxicity study in Sprague-Dawley Spartan rats (MRID 099640, 242150; Doc. No. 001571), technical chlorpyrifos-methyl was administered on gestation days 6-15 by gavage in corn oil at dose levels of 50, 100, or 200 mg/kg/day. The maternal NOEL was 100 mg/kg/day, and the maternal LOEL was 200 mg/kg/day, based on decreased body weight. The developmental LOEL was 50 mg/kg/day (the LDT, based on delayed ossification of sternebrae; no developmental NOEL was identified. At 200 mg/kg/day, there was also an increase in the incidence of lumbar ribs or spurs (i.e., extra 14th ribs). The DER notes that the control incidence of these findings was low as compared to the historical incidence. Neither maternal nor fetal cholinesterase levels were measured in this study. (1973)

In a prenatal developmental toxicity study conducted in Japan white rabbits (10/group) (MRID 099640, 242150; Doc. No. 001571, 002632), technical chlorpyrifos-methyl was administered by gavage in corn oil at doses of 4, 8, or 16 mg/kg/day on gestation days 6-18. The maternal NOEL was 4 mg/kg/day, based upon 20% decreased food consumption during treatment at the maternal LOEL of 8 mg/kg/day and above, with posttreatment recovery. The DER states that the developmental NOEL was also 4 mg/kg/day, based upon a decreased number of corpora lutea, surviving fetuses and number of implantations at 8 mg/kg/day (the developmental LOEL) and above. 1) Since the decrease in number of corpora lutea is unlikely to be a treatment-related effect (because the does were not dosed prior to impregnation), the cesarean section and fetal data were reexamined. There did not appear to be any treatment-related effect on any fetal parameters. 2) It was noted that in a dose range-finding study in rabbits, 8, 16, or 32 mg/kg/day was administered by gavage to rabbits for 14 days. Plasma ChE levels were measured at day 1 and 13 of study, and were found to be decreased at 16 mg/kg/day and above by day 1. This information was not reported in the original DER. (1976)

Recommendation for a developmental neurotoxicity study: *The following information* was considered in support of the need for a developmental neurotoxicity study for chlorpyrifos-methyl:

1) Evidence that support requiring a developmental neurotoxicity study:

» Chlorpyrifos-methyl is a neurotoxic chemical.
- SAR: chlorpyrifos-methyl is an organophosphate.
- Administration to various species (rat, mouse, dog, monkey, human) results in ChE inhibition in the plasma and erythrocytes (brain cholinesterase is seldom affected). Guideline neurotoxicity studies in the rat (acute and subchronic) have not been submitted to the Agency.
- Positive delayed neurotoxicity was observed in the hen following a single oral dose of chlorpyrifos-methyl, although at a very high dose level (5000 mg/kg).

2) Evidence that do not support asking for a developmental neurotoxicity study:

» No evidence of abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic oral doses up to 250 or 16 mg/kg/day, respectively.

» Neither brain weight nor histopathology of the nervous system were affected in the subchronic and chronic toxicity studies in several species.

» Chlorpyrifos-methyl is not very acutely lethal, with oral LD50 values in the rat that are greater than 2000 mg/kg for males and 1600 mg/kg for females, LD50 values for the guinea pig of 2250 mg/kg, and LD50 values in the chicken of 7500 mg/kg or greater. Toxicity at lower doses appears to consist primarily of cholinesterase inhibition.

3) Unknown:

» No acute or subchronic neurotoxicity studies were conducted in the rat, to determine whether

or not histopathology will occur in that species when examined following perfusion of tissues.

FQPA assessment of additional sensitivity for infants and children:

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for chlorpyrifos-methyl was evaluated by the Hazard Identification SARC.

Adequacy of data: The data package included acceptable two-generation reproduction study in rats and prenatal developmental toxicity studies in rats and rabbits, meeting the basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. There are no data gaps for the assessment of the effects of chlorpyrifos-methyl following *in utero* and/or early postnatal exposure.

Susceptibility issues: In the three-generation reproduction study in rats and the prenatal developmental toxicity study in rabbits, there was no indication of increased sensitivity of the young animals to pre-and/or postnatal exposure to chlorpyrifos-methyl. However, in the prenatal developmental toxicity study in rats, developmental toxicity was observed at a dose (50 mg/kg/day) that was not maternally toxic (the maternal NOEL was 100 mg/kg/day), indicating a possible increased sensitivity to the developing offspring following *in utero* exposure.

Uncertainty factor: The Committee determined that for chlorpyrifos-methyl the 10-fold uncertainty factor for the protection of infants and children would be , based upon the following information:

1. There are no data gaps for the assessment of the effects of chlorpyrifos-methyl on young animals in the standard required studies. Acceptable prenatal toxicity studies in rats and rabbits, and an acceptable three-generation reproduction study in rats have been received by the Agency. However, there is insufficient information available to determine if a developmental neurotoxicity in rats should be conducted with chlorpyrifos-methyl; the acute and subchronic toxicity studies in rats have not been submitted to the Agency.
2. There is an indication of additional sensitivity to young rats following prenatal

exposure to chlorpyrifos-methyl. Although a similar sensitivity did not occur in rabbits following in utero exposure, nor did it occur in the three-generation reproduction study in rats following pre- and postnatal exposure. (It must be considered though that the studies that did not identify additional sensitivity to the offspring were conducted in a different species, or were administered by a different route of administration with measurement of very different toxicological endpoints.) No comparative studies of cholinesterase inhibition in the adults and offspring were conducted to further clarify this point.

3. Delayed neurotoxicity was observed in the chicken following acute exposure with chlorpyrifos-methyl, albeit at extremely high doses (5000 mg/kg/day).

REFERENCES:

No additional references from the open literature were identified.

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Chemical:	**Chlorpyrifos-methyl (ANSI)**
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HED File Code	~~**14000 Risk Reviews**~~ 13000 Tox Review
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